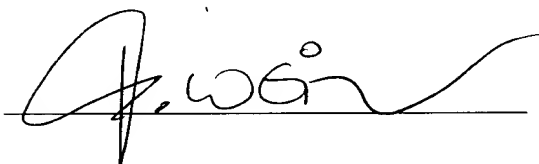


DECLARATION

I, Andrea Weini, of Vossius & Partner, Siebertstr. 4, 81675 Munich, Germany, hereby declare that I am conversant with the English and German languages and am the translator of the document attached and certify that to the best of my knowledge and belief the following is a true and correct English translation of the Swiss priority document 19990051.

Signed this 12th day of July 2002

A handwritten signature in black ink, appearing to read 'A. Weini', is written over a horizontal line.

ENGLISH TRANSLATION OF THE PRIORITY DOCUMENT

Novel use of antibodies and their derivatives in the active specific immunotherapy against cancer

Description

Antibodies against tumour-associated antigens or their derivatives having the same idio type can be used for the vaccination against cancer.

With the discovery of the hybridoma technology, it became possible to generate monoclonal antibodies (MAB) against the most varied antigens. This technology which can generally be applied to all biological problems also plays an important role in cancer research. Over the last twenty years, MAB directed against a multitude of tumor-associated antigens (TAA) have been produced. TAA are structures which are expressed predominantly on the cell membrane of tumor cells and which, thus, allow differentiation from non-malignant tissue. Therefore, they are regarded as targets for diagnostic or therapeutic applications on the basis of specific MAB or derivatives derived from these MAB.

Direct therapeutic applications of MAB which are directed against TAA are based on passive immunotherapies, i.e. an MAB or a derivative is applied systemically to cancer patients in a suitable amount and has a therapeutic effect only as long as the concentration in the organism is sufficiently high. The biological half-life of such agents depends on their structure and ranges from only a few hours to several days. It is therefore necessary to repeat the applications. However, if xenogenic antibodies (e.g. murine MAB) are used, this leads to unwanted immune reactions, which can lead to the neutralization of a possible therapeutic effect and to dangerous side effects (anaphylactic shock). Therefore, such immunotherapeutics can only be administered for a limited period of time.

Another approach for the immunotherapy of cancer is based on the selective activation of the immune system of cancer patients so as to combat malignant cells

for which the most varied types of cancer vaccines are used. These include vaccinations with autologous or allogenic tumor cells, vaccinations with autologous or allogenic tumor cells which have been chemically modified or which have been modified by gene technological techniques, vaccinations with isolated TAA or TAA which have been produced using chemical or gene technological methods, with peptides derived therefrom, and, recently, also vaccinations with DNAs coding for TAA or structures derived therefrom, etc. An alternative method is based on the use of anti-idiotypic antibodies for the vaccination against cancer. Suitable anti-idiotypic antibodies can immunologically mimic a TAA. As xenogenic proteins (e.g. murine antibodies, goat antibodies etc.) they induce a strong immune response in human after vaccination – in contrast to the proper human tumor antigens, which, as structures of the self, are often immunogenic to a low degree only. Therefore, anti-idiotypic antibodies can be used for vaccination as an immunogenic substitute for a tumor antigen.

In contrast to the passive immunotherapy with anti-tumor antibodies in the active specific cancer immunotherapy, even very small amounts of a suitable vaccine are, in principle, sufficient to induce an immunity which lasts for months or for years and which can be boosted by repeated vaccinations if it weakens. Moreover, active immunization allows to induce a humoral as well as a cellular immunity the cooperation of which can lead to an effective protection.

In summary, the use of antibodies or their derivatives for immunotherapy against cancer, which has been described so far, is essentially based on two principles:

- passive therapy with antibodies or their derivatives which are directed against TAA.
- active immunization (vaccination) with antibodies or their derivatives which are directed against the idiotype of antibodies having a specificity against TAA.

In the course of the discovery and the subsequent characterization of the most varied TAA, it has turned out that they have important functions as regards cancer cells. They enable the degenerate cells to show properties characteristic of the malignant phenotype, such as an increased capability for adhesion, which play an important role in establishing metastases. However, such antigens can, at certain stages, also be expressed on normal cells where they are responsible for the normal functions of these cells. Without laying claim to completeness, some examples of such antigens are listed in the following:

- N-CAM (Neuronal Cell Adhesion Molecule), which is often expressed on

tumors of neuronal origin and which effects homophilic adhesion (J. Cell Biol. 118 (1992), 937).

- The Lewis Y carbohydrate antigen, which occurs on the majority of tumors of epithelial origin, but which also plays an important role during the fetal development of epithelial tissues. It has been shown that the expression of this antigen in lung cancer is strongly associated with an unfavorable prognosis since Lewis Y positive cancer cells obviously have a higher metastatic potential (N. Engl. J. Med. 327 (1992), 14).
- CEA (Carcino Embryonic Antigen), which often occurs on epithelial tumors of the gastrointestinal tract and which has been identified as a self-adhesion molecule (Cell 57 (1989), 327).
- Ep-CAM (Epithelial Cell Adhesion Molecule), which is expressed on nearly all tumors of epithelial origin, but which also occurs on a large number of normal epithels. It has been characterized as a self-adhesion molecule and can therefore be classified as a pan-epithelial adhesion antigen (J. Cell Biol. 125 (1994), 437).

The present invention relates to new applications of antibodies or their derivatives which are directed against TAA. These new therapeutic applications differ substantially from the two basic possibilities of therapeutic application which have been mentioned earlier and which have been known so far.

The binding region of an antibody against a TAA can represent a structural complementary picture of the binding epitope of the respective TAA according to the "lock and key" principle. This means that such an antibody has, in its idiotype, a structural information of the epitope of the TAA against which it is directed. Thus, if a cancer patient is vaccinated with a suitable immunogenic antibody against a TAA (i.e. for example with a murine MAB against a TAA), antibodies are produced in the patient which, in part, are directed against the idiotype of the antibody used as vaccine and which can structurally mimic the epitope of the TAA according to the "lock and key" principle. This means that due to such a vaccination, so to say, soluble variants of the epitope of the TAA are generated in the cancer patient, which can be effective as actively induced autologous antibodies for a long period of time and the titer of which can be boosted in suitable intervals by repeated vaccinations. The physiological effect of an immune response induced by vaccination with an antibody directed against a TAA naturally depends on the function of the respective TAA. If the TAA has, for example, the function of a receptor for the adhesion of tumor cells to a ligand on endothelial cells of the vascular system (such a property is important for the ability of the disseminated tumor cells to exit from the vascular system and to settle in tissue in order to form a metastasis), this ability for

adhesion is reduced by vaccination with a suitable antibody directed against this TAA, since induced antibodies, which will compete for the interaction of the TAA with its ligand as they mimic the TAA in soluble form, will be permanently present in the circulation and the tissue.

Generally spoken, it is possible, according to the explanations given above, to achieve by vaccination with suitable antibodies against TAA which have a function as regards the malignity of tumor cells, that the induced immune response interferes with the function of the TAA in its interaction with its ligand and hampers or prevents this interaction. This means that cancer cells can not or not sufficiently express properties which are important for the malignant phenotype, which makes it possible to slow down or stop the development of the disease and to suppress the development of metastases, in particular, at an early stage.

A special situation occurs if the TAA exerts the function of self-adhesion. In such cases, certain epitopes of the TAA are obviously responsible for the homophilic binding to the same TAA on a different cell. Examples of such TAA are, inter alia, N-CAM (Neuronal Cellular Adhesion Molecule), CEA (Carcino Embryonic Antigen) and Ep-CAM (Epithelial Cell Adhesion Molecule). Antibodies directed against epitopes of self-adhesion antigens which are involved in this function, can, as described above, contain a structural information complementary to such an epitope. By vaccination with such antibodies, it is thus possible, as described above, to induce the formation of antibodies which have the property of this self-adhesion in the binding reaction. This means that such induced antibodies can, in turn, bind to the self-adhesion TAA since in such a case receptor and ligand are identical. Thus, it is possible to induce an immune response by vaccination of cancer patients with suitable antibodies directed against self-adhesion TAA, wherein said immune response in turn directly binds to tumor cells and thereby triggers various therapeutic effects. On the one hand, the ability of self-adhesion, which is important to malignant cells, is blocked and, on the other hand, human effector functions such as complement-dependent lysis and/or lysis due to activation of cytotoxic effector cells, can be triggered by the binding of the induced antibodies to the tumor cells, which lead to the destruction of the tumor cells.

By all the above mentioned mechanisms and effects, the formation of new metastases can be suppressed and the dissemination of the disease can, at least, be slowed down thanks to vaccination of cancer patients with suitable antibodies against TAA. In early stages of the disease, for example after a successful operation of a primary tumor (adjuvant stage), remaining disseminated tumor cells are prevented

from establishing themselves as new metastases due to such vaccinations. This allows to prolong the relapse-free survival period and therefore the overall lifetime of such patients. It may optionally be possible to obtain a lifelong protection against the formation of metastases due to such vaccinations and booster vaccinations which are carried out in suitable intervals. Of particular interest are vaccinations of cancer patients with suitable antibodies directed against a self-adhesion TAA since in these cases, as described above, it is possible to achieve an enhanced therapeutic effect due to an additional direct attack of the induced immune response on the tumor cells.

The therapeutically effective immune response which is induced by the vaccination with suitable antibodies directed against TAA is determined by the binding region of these antibodies, i.e. by their idiotype. Therefore, it is, in principle, also possible to use, instead of intact antibodies, fragments or derivatives of these antibodies for a successful vaccination as long as these derivatives still contain the idiotype of the respective starting-antibody. As examples, without being limiting, can be listed: $F(ab)_2$ fragments, $F(ab)'$ fragments, Fv fragments which can be produced either by known biochemical methods (enzymatic cleavage) or by known methods of molecular biology. Further examples are derivatives of antibodies, which can be produced according to known chemical, biochemical or gene technological methods, e.g. antibodies amidated with fatty acids via the free amino positions in order to increase the lipophilia for incorporation into liposomes.

As is frequently common with vaccines, suitable antibodies directed against TAA or their fragments and derivatives may be formulated together with vaccine adjuvants. It is possible to enhance the immune response by such adjuvants. As examples of adjuvants, however not being limited to these, the following can be listed: aluminium hydroxide (Alu gel), derivatives of lipopolysaccharides, Bacillus Calmette Guerin (BCG), liposome preparations, formulations with additional antigens against which the immune system has already produced a strong immune response, such as for example tetanus toxoid or constituents of influenza viruses, optionally in a liposome preparation.

Cancer cells often express several TAA at the same time against which suitable antibodies for vaccination are either available or can be generated. In order to obtain an enhanced or possibly synergistic effect of the induced immune response and to minimize the potential danger of the selection of antigen-negative variants and in order to counteract a possible tumor cell heterogeneity, it may be advantageous to use a combination of two or more suitable antibodies or their fragments or derivatives simultaneously for vaccination.

The use of suitable antibodies directed against TAA or of their derivatives or fragments as vaccines differs substantially from the known applications of such anti-TAA antibodies for the passive immunotherapy. Some essential advantages of the use according to the invention are summarized as follows:

Antibodies directed against TAA for the passive immunotherapy of cancer:

- high dosage (≥ 100 mg / infusion)
- short effect due to elimination of the effective agent
- xenogenic antibody undesirable due to immunogenicity
- the duration of the therapy is limited, in particular in the case of xenogenic antibodies

Antibodies directed against TAA for the therapeutic vaccination against cancer:

- low dosage (< 1 mg / vaccination)
- long lasting effect of the directly induced immune response
- xenogenic antibodies desirable since the effect is based on immunogenicity
- duration of the treatment unlimited (booster vaccinations)

In the following, experiments will be described which show that the vaccination with a certain murine MAB (HE2), which is directed against the self-adhesion TAA Ep-CAM, or the vaccination with its F(ab)₂ fragment directly leads to the induction of antibodies which selectively bind on human tumor cells carrying this antigen. This shows, as an example but without any limitation, that an immune response which can have a therapeutic effect in cancer diseases is induced by vaccination with suitable antibodies directed against a self-adhesion TAA or with their derivatives which, at least, comprise the idiotype of the starting antibody.

The murine monoclonal antibody HE2 was generated according to described standard procedures of the hybridoma technology (see, e.g., H. Zola. Monoclonal Antibodies: A Manual of Techniques. CRC Press, Inc. ISBN 0-8493-6476-0; 1988). Balb/c mice were immunized with human colorectal cancer cells according to standard protocols. The spleen cells were fused with the mouse melanoma line P3X63Ag8 and hybridomas were selected which produce antibodies which selectively bind to human epithelial cancer cells but not to WM9 melanoma cells. Finally, a hybridoma was selected which secretes an IgG2a/kappa antibody. This

antibody, which was called HE2, binds to Ep-CAM as was shown by Western Blot analysis with membrane preparations from KATO III stomach cancer cells using a known anti-Ep-CAM antibody (KS1-4) as a comparison.

In the Examples which are listed below and which are to illustrate the present invention but not to limit it, the following materials were used:

microtiter plates:	Immunoplates II (Nunc)
cell lines:	KATO III: human stomach cancer cell line, Ep-CAM positive (ATCC HTB 103) WM 9: human melanoma cell line, Ep-CAM negative
Medium A:	RPMI 1640 + 2 g/l NaHCO_3 100 U/ml penicillin G 100 $\mu\text{g/ml}$ streptomycin sulfate 4 mM glutamine 10 % fetal calf serum (heat inactivated)
Binding buffer:	15 mM Na_2CO_3 35 mM NaHCO_3 3 mM NaN_3 pH value: 9.6
PBS deficient:	138 mM NaCl 1.5 mM KH_2PO_4 2.7 mM KCl 6.5 mM Na_2HPO_4 pH value: 7.2
Fixing solution:	0.1 % glutardialdehyde in physiological NaCl solution
Washing buffer A:	2% NaCl 0.2% Triton X-100 in PBS deficient
Washing buffer B:	0.05 % Tween 20 in PBS deficient
Blocking buffer A:	5 % fetal calf serum (heat inactivated)

	in PBS deficient
Blocking buffer B:	1 % bovine serum albumin 0.1 % NaN ₃ in PBS deficient
Dilution buffer A:	2% fetal calf serum (heat inactivated) in PBS deficient
Dilution buffer B:	PBS deficient
Staining buffer:	24.3 mM citric acid 51.4 mM Na ₂ HPO ₄ pH value: 5.0
Substrate:	40 mg o-phenylene diamin dihydrochloride 100 ml staining buffer 20 μ l H ₂ O ₂ (30%)
Stop solution:	4 N H ₂ SO ₄

For being able to analyse the direct humoral immune response to the vaccination with the F(ab)'₂ fragment of the murine MAB HE2, goats were immunized with this fragment. The fragment was produced by cleavage of HE2 with pepsin and purified according to methods which are known per se and which have been described. Two goats were vaccinated intradermally at multiple sites with 1.5 mg of the F(ab)'₂ fragment in 3 ml PBS deficient together with 3 ml of Freund's Complete Adjuvant (Difco). On day 8, a first booster vaccination as on day 1 was given, however with Freund's Incomplete Adjuvant (Difco). On day 29, a second booster vaccination was given in the same manner. However, no adjuvant is added. Blood was taken before the start of the vaccination and on day 54 for the recovery of serum for the analysis of the immune response developed.

The goat immunoserum which was recovered and pooled was first analysed for immunoglobulins which are directed against the MAB HE2 in comparison with a pre-serum in order to determine the total immune response of the goats vaccinated. This analysis was carried out as follows by means of an ELISA test:

100 μ l aliquots of the MAB HE2 (solution with 10 μ g/ml in binding buffer) are

incubated in the wells of a microtiter plate for 1 hour at 37°C. After washing the plate with washing buffer A six times, 200 μ l of the blocking buffer A are added to each well and the plate is incubated for 30 minutes at 37°C. After washing the plate as described above, 100 μ l aliquots of the goat sera to be tested are incubated in dilutions from 1:100 to 1:1,000,000 in dilution buffer A for 1 hour at 37°C. After washing the plate as described above, 100 μ l of the peroxidase-conjugated rabbit anti-goat-Ig antibody (Zymed) are added to each well at a dilution of 1:1,000 in dilution buffer A and are incubated for 30 minutes at 37°C. The plate is washed four times with washing buffer A and twice with staining buffer. The binding of the antibody is detected by addition of 100 μ l of the specific substrate to each well and the staining reaction is stopped after about 3 minutes by addition of 50 μ l stop solution. The evaluation is carried out by measuring the optical density (OD) at 490 nm (wavelength of the reference measurement is 620 nm).

The result of this experiment is shown in Figure1: by the vaccination with the F(ab)'₂ fragment of the MAB HE2, the goats have developed a strong immune response, whereas no antibodies directed against HE2 are found in a pre-serum.

Then, it was analysed whether immunoglobulins could be detected in the goat immunoserum which bind to human cancer cells which express the TAA against which the MAB HE2 is directed (Ep-CAM). For this purpose, the KATO III stomach cancer cell line was used. As a control, the binding to a human cell line was tested, too, which does not express Ep-CAM (WM9 melanoma cells). These analyses were carried out as follows by means of cell-ELISA tests:

The wells of a microtiter plate are incubated at +4°C over night with 100 μ l of a cell suspension of the cell line to be tested at a concentration of 2×10^6 cells/ml in medium A. After sucking off the supernatant, the plate is incubated with 50 μ l fixing solution per well for 5 minutes at room temperature. After sucking off the supernatant, 200 μ l blocking buffer B are added to each well and the plate is incubated for 1 hour at 37°C. After washing twice with 200 μ l washing buffer B, 100 μ l aliquots of the goat sera to be tested are incubated for 1 hour at 37°C at dilutions of 1:10 to 1:100,000 in dilution buffer B. After washing the plate twice with 100 μ l ice-cold washing buffer B, 100 μ l of the peroxidase-conjugated rabbit anti-goat-Ig antibody (Zymed) are added at a dilution of 1:1,000 in dilution buffer A and are incubated for 45 minutes at 37°C. The plate is washed three times with 100 μ l ice-cold washing buffer B. The binding of the antibody is detected by the addition of 100 μ l of the specific substrate per well and the staining reaction is stopped after about 5 minutes by addition of 50 μ l stop solution. The evaluation is carried out by measuring the optical density (OD) at 490

nm (wavelength of the reference measurement is 620 nm).

The result of these experiments is shown in Figures 2 and 3: The goat immunoserum contains immunoglobulins which strongly bind on the Ep-CAM-positive KATO cells, whereas no binding is detected on the Ep-CAM-negative WM9 cells. There are no antibodies which bind to these cells in the pre-serum. This very surprising result shows that antibodies formed by the vaccination with the HE2-F(ab)₂' fragment are in fact capable of binding to cells expressing the TAA which is recognised by HE2. The function of the TAA with regard to the self-adhesion could obviously be transferred to the antibodies formed by the vaccination with HE2, as has been explained before in detail.

For proving that the antibodies which were formed in the goats by the vaccination with the F(ab)₂' fragment of HE2 and which are directed against the idiotype of this MAB are, in fact, the antibodies which bind to the KATO cells, the anti-idiotypic portion of these induced antibodies was specifically purified from the goat immunoserum by means of a sequence of immunoaffinity chromatographies, as is principally described (Proc. Natl. Acad. Sci. USA 81:216, 1984). The sequence of the purification steps is summarised again as follows: In a first step, a purification of the total IgG contained in the goat serum was carried out according to known methods on a DEAE anion exchanger column. Subsequently, the goat antibodies which are directed against constant regions of the F(ab)₂' fragment of HE2 were bound to an immunoaffinity column (CH-Sepharose 4B, Pharmacia) to which irrelevant murine IgG2a was coupled, whereas the fraction of the anti-idiotypic goat antibodies does not bind to this column. Therefore, in a last step, the flow-through of this immunoaffinity chromatography was bound to an immunoaffinity column (CH-Sepharose 4B, Pharmacia) to which HE2 was coupled. The fraction specifically bound to this column was eluted with a buffer pH 2.8 (0.1 M glycine/HCl) and neutralized. The goat IgG fraction obtained in this way is directed against the idiotype of HE2. These affinity-purified goat antibodies were again analysed for binding to the EP-CAM-positive KATO cells as well as to the Ep-CAM-negative WM9 cells. The determination was, in principle, carried out as has been described above with regard to goat serum Ig. Instead of serum dilutions, concentrations of 100 µg/ml to 0.031 µg/ml of the immunoaffinity-purified goat IgG and of unspecific purified goat IgG, respectively, were used.

The result of these experiments is shown in Figures 4 and 5: the goat IgG which is directed against the idiotype of HE2 strongly binds to the Ep-CAM-positive KATO cells, whereas the unspecific goat IgG hardly binds. The binding of the affinity-

purified goat IgG to the Ep-CAM-negative WM9 cells, however, does not differ from the binding of the unspecific goat IgG. It has therefore been proved that the antibodies which are formed directly by the vaccination with the F(ab)₂ fragment of HE2 which are directed against the idiotype of this antibody also bind to cancer cells expressing the TAA which is recognised by HE2.

Then, due to the aforementioned results of the goat vaccination, a patient suffering from intestinal cancer with metastases (Dukes D) was vaccinated with the MAB HE2 in an anecdotal case. For this purpose, the following formulation was used:

0.83 ml of a suspension of Alu-Gel (Alu-Gel S by Serva, 2% suspension, quality degree: adjuvant for the preparation of vaccines) was carefully agitated for 1 hour at room temperature under sterile conditions with 0.5 ml of a solution of 10 mg/ml HE2 together with 3.67 ml PBS def. (final concentration of HE2: 1 mg/ml; Alu-Gel S: 0.33%). Then, the suspension was sterily filled in injection vials at aliquots of 0.5 ml.

The patient was vaccinated subcutaneously four times altogether with 0.5 ml of this suspension (corresponds to 0.5 mg HE2) (day 1, 50, 78, 114). Before every vaccination and on day 128, blood was taken for recovery of serum. First, it was investigated whether antibodies binding to the KATO III cells were induced by the vaccinations. For these tests, too, the cell-ELISA was used which was carried out with the sera obtained at the different times as described above with the exception that a peroxidase-conjugated goat-anti-human-Ig antibody (Zymed) was used for the detection.

The results of these experiments are shown in Figure 6. In this cancer patient, substantial titers of antibodies binding to the KATO cells are obviously induced by the vaccinations.

Furthermore, it was analysed whether the antibodies induced by the vaccination with HE2 mediate a cytotoxic effect against KATO III cancer cells *ex vivo*. For this purpose, KATO III cells were incubated with pre-serums and immunoserums of this cancer patient in order to show a complement-dependent lysis mediated by the antibodies induced. The following steps were taken in accordance with the methodology known *per se*:

One day before carrying out the test, KATO III cells are transferred to fresh medium A and are kept in a cell culture flask at 37°C/5% CO₂. On the next day, the cells are first labelled with ⁵¹chrome. 5x10⁶ cells are incubated in 800 µl medium A at 37°C/5% CO₂ with 100 µCi Na₂⁵¹CrO₄. Subsequently, the cells are washed with medium A and

adjusted to a density of 2.5×10^5 cells/ml. 100 μ l aliquots of this cell suspension are pipetted into the wells of a microtiter plate. 100 μ l aliquots of the patient sera to be tested are added and incubated for 3 hours at 37°C/5% CO₂. The supernatants are recovered by using a Skatron-Harvesting-Press and are measured in a gamma-counter. As a result, the values for the "experimental release" are obtained. For the determination of the "total release", the cells are treated as described above wherein serum is replaced by a solution of 2% SDS, 50 mM Na₂CO₃ and 10 mM EDTA. The values for the "spontaneous release" are obtained by replacing serum by medium A. The result is calculated as follows:

$$\% \text{ Lyse} = \frac{\text{experimental release} - \text{spontaneous release}}{\text{total release} - \text{spontaneous release}} \times 100$$

The test is carried out 3 times and the mean value and the standard deviation of the single results are indicated.

The results are shown in Figure 7. The antibodies induced by the vaccination with HE2 are obviously capable of destroying Ep-CAM-positive KATO III cells in autologous patient serum by means of complement-dependent lysis.

Due to the experiments described, it could be shown exemplarily that the vaccination with suitable antibodies against a self-adhesion TAA, such as, e.g., Ep-CAM or their derivatives having the same idiotype as the respective starting antibody trigger a humoral immune response which selectively binds on tumor cells expressing said self-adhesion TAA. The antibodies induced have a cytotoxic potential against such tumor cells. A vaccination with such an antibody can, therefore, lead to a therapeutic effect in cancer diseases.

Claims

1. Use of antibodies which are directed against human cellular membrane antigens or of their derivatives having the same binding specificity and, optionally, of their combinations for the vaccination against cancer.
2. Claim according to 1, wherein the cellular membrane antigens play a role in adhesion processes.
3. Claim according to 1 or 2, wherein the cellular membrane antigens are membrane antigens of epithelial cells.
4. Claim according to 1 to 3, wherein the cellular membrane antigen is a homophilic cell adhesion molecule.
5. Claim according to 4, wherein the cellular membrane antigen is the Epithelial Cellular Adhesion molecule (Ep-CAM).
6. Claim according to 1 to 5, wherein the antibodies are preferred to be monoclonal antibodies of animal origin.
7. Claim according to 1 to 5, wherein the antibody derivatives are molecules produced chemically, biochemically or by methods of molecular biology, wherein said molecules contain at least the idiotype of the starting antibody.
8. Claim according to 5, wherein the antibody is the murine monoclonal antibody HE2.
9. Claim according to 1 to 8, wherein the antibodies or their derivatives having the same specificity are formulated with a suitable vaccine adjuvant, such as, e.g., aluminium hydroxide, according to methods known per se in such a way that an enhanced immune response is triggered in a human.
10. Claim according to 1 to 8, wherein the vaccine adjuvant used for formulating the antibodies or their derivatives is a liposome preparation together with immunogenic proteins such as, for example, proteins of influenza viruses.

Abstract

Antibodies against tumor-associated antigens or their derivatives having the same idiotype can be used for the vaccination against cancer.

Figure 1

Vaccination of goats with HE2-F(ab)'₂:
Serum Ig with specificity for HE2

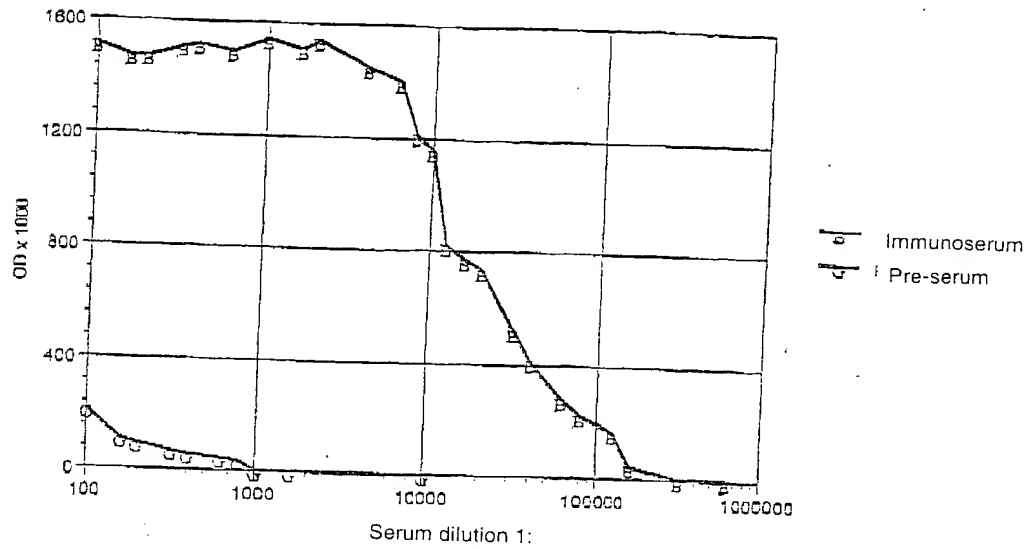


Figure 2

Vaccination of goats with HE2-F(ab)'₂:
Binding of serum Ig to Ep-CAM positive
human stomach cancer cells (KATO III)

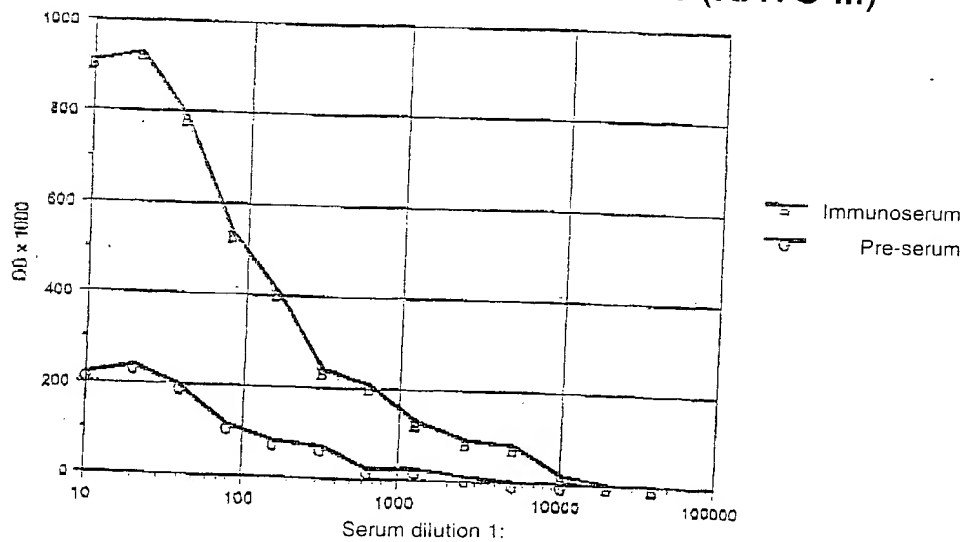


Figure 3

**Vaccination of goats with HE2-F(ab)'₂:
Binding of serum Ig to Ep-CAM negative
human melanoma cells (WM9)**

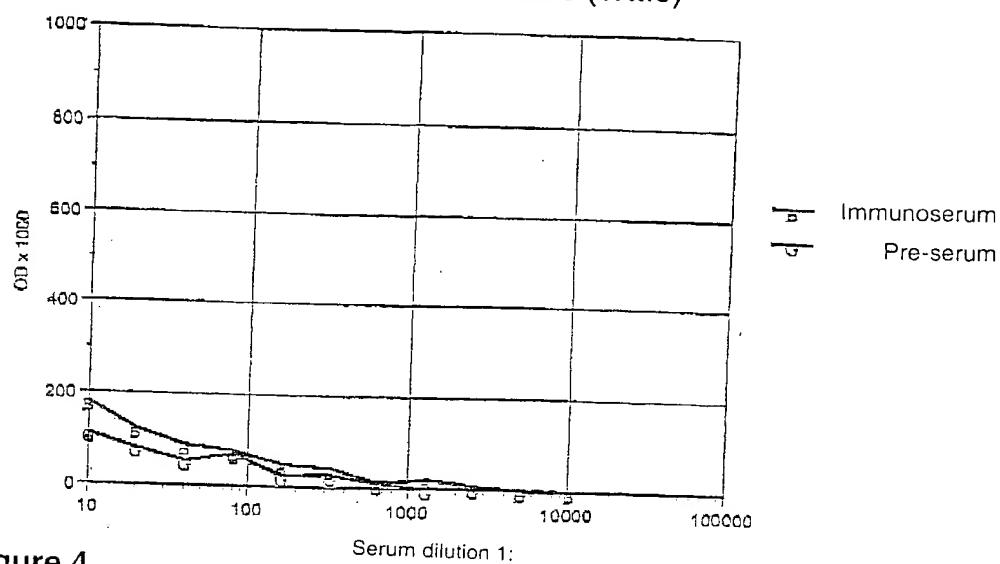


Figure 4

**Vaccination of goats with HE2-F(ab)'₂:
Binding of affinity-purified serum Ig to Ep-CAM positive
human stomach cancer cells (KATO III)**

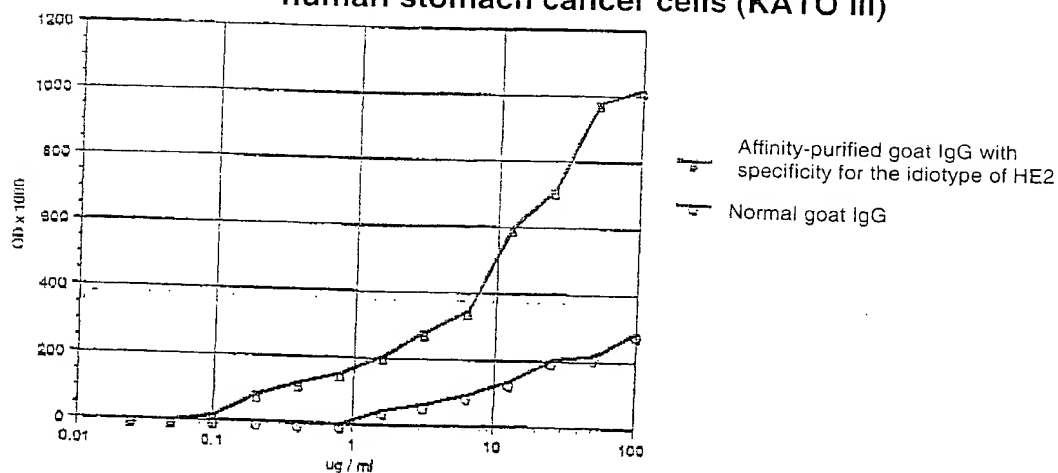


Figure 5

Vaccination of goats with HE2-F(ab)₂:
Binding of affinity-purified serum Ig to Ep-CAM negative
human melanoma cells

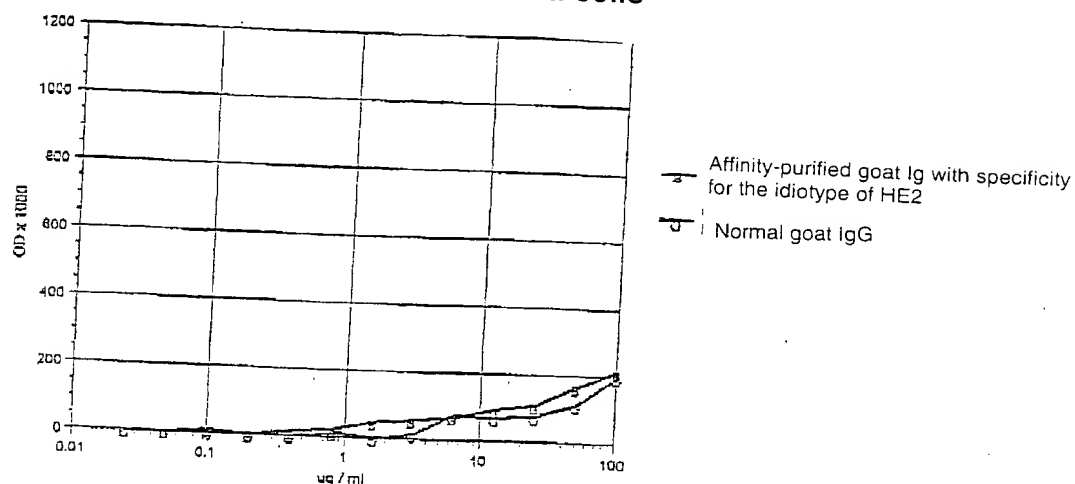


Figure 6

Vaccination of a patient with intestinal cancer with HE2:
Induction of antibodies against human
stomach cancer cells (KATO III)

